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G. CARROLL HILMAN

B.S., Louisiana State University, 1921
M.S., University of Iowa, 1922

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DISSERTATION

SUBMITTED TO THE FACULTY OF THE GRADUATE COLLEGE OF THE STATE UNIVERSITY OF IOWA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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NEW DERIVATIVES OF VANILLIN AND SOME OF THEIR REACTIONS

By G. Carroll Hilman

The simplest derivatives of vanillin on record are the monohalogenated and mononitro substitution products. Carles[1] obtained a mono-iodo-vanillin as early as 1872, but did not prove its structure. Hann[2] assumes that iodine occupies Position 5 (CHO = 1) in that product. Tiemann

[1] Carles, *Bull. soc. chim.*, **17**, 14 (1872).

[2] Hann, *J. Am. Chem. Soc.*, **47**, 2000 (1925).

and Haarmann[3] prepared a monobromo derivative, the structure of which has been established by Dakin[4] and by Brady and Dunn[5] to be 5-bromovanillin. In a recent report from this Laboratory[6] the two other possible monobromo substitution products of vanillin, the 2 and 6 derivatives, respectively, have been described. Peratoner[7] obtained a chlorine derivative which melted at 158–160° and for which he recorded a chlorine content of 20.5% (calcd., 19.0). This may have been an impure sample of the monochlorovanillin, m. p. 165°, isolated by Hann[2] and which probably has chlorine in Position 5.[8] Examination of the literature shows that these derivatives have been studied too little to indicate what effect the halogen substituent will have on the aldehyde in the usual reactions. To characterize 5-bromovanillin further, and to familiarize ourselves with its general behavior, we studied the derivatives indicated in Table I.

TABLE I

DERIVATIVES OF 5-BROMOVANILLIN[a]

Compound	Formula	Solvent	Crystal form	M. p., °C.	Analysis Subs., g.	AgBr, g.	Halogen, % Calcd.	Found
5-Bromovanillidene-aniline	$C_{14}H_{12}O_2NBr$	Abs. alcohol	Canary-yellow rods	124	0.3395	0.2080	26.14	26.07
5-Bromovanillidene-*p*-toluidine	$C_{15}H_{14}O_2NBr$	Abs. alcohol	Yellow plates	159–160	.2977	.1734	25.00	24.78
5-Bromovanillidene-tolidine[b]	$C_{22}H_{21}O_2N_2Br$	Pyridine and alcohol	Yellow powder	184–185	.3327	.1447	18.82	18.51
5-Bromovanillin-phenylhydrazone	$C_{14}H_{13}O_2N_2Br$	Alcohol	Light brown needles	117	.3698	.2149	24.92	24.73
5-Bromovanillin-*p*-bromophenylhydrazone	$C_{14}H_{12}O_2N_2Br_2$	90% acetic acid	Cream-colored needles	153	.2738	.2602	40.00	40.43
5-Bromovanillin semicarbazone[c]	$C_9H_{10}O_3N_3Br \cdot C_2H_5OH$	Alcohol	Amber rods	185–186	.2375	.1328	23.95	23.80

[a] 5-Bromovanillin crystallizes in plates from acetic acid, if left undisturbed. From alcohol, both needles and plates were observed.

[b] This compound appeared to combine with pyridine upon crystallization, but attempts to determine the amount were unsatisfactory.

[c] When a portion of this material was heated to constant weight at 105°, it left a residue that melted at 189–190°. 0.2834 g. of substance left 0.2438 g. of residue. Calcd. for C_2H_5OH: 13.77. Found: 13.97.

Several interesting observations were made in this part of the work. In the condensation with amino compounds it was found that pyridine[9]

[3] Tiemann and Haarmann, *Ber.*, **7**, 615 (1874).

[4] Dakin, *Am. Chem. J.*, **42**, 493 (1909).

[5] Brady and Dunn, *J. Chem. Soc.*, **107**, 1859 (1915).

[6] Raiford and Stoesser, *J. Am. Chem. Soc.*, **49**, 1077 (1927).

[7] Peratoner, *Gazz. chim. ital.*, **28** [1], 235 (1898).

[8] Schniter [*Ber.*, **20**, 1317 (1887)] found in work on thymoquinone that the position taken by chlorine is sometimes not the same as that taken by bromine.

[9] This solvent was tested here because it was found in preliminary trials with dibromovanillin (see below) that the latter is almost insoluble in alcohol.

could replace alcohol, the solvent usually employed. Hydrazones were obtained in acetic acid solutions of 90% up to glacial, although a concentration of 50% or less is generally employed.[10] In some instances the compounds combined with a portion of the solvent on crystallization. The semicarbazone united with one molecular proportion of alcohol, and it was shown that vanillidene-tolidine combined with pyridine when crystallized from the latter, but a definite proportion was not established. Attempts to cause 5-bromovanillin to undergo the benzoin condensation have thus far been unsuccessful.[11]

A second point of interest in this work was to study further the extent to which substituents in the *ortho* positions as respects the reacting groups (amino and aldehyde) will interfere in the formation of benzylidene compounds. Hantzsch[12] noted that *sym.*-tribromo- and trinitro-anilines do not condense with benzaldehyde. Other than the single instance reported by Blanksma[13] in which he found that 2,4,6-tribromobenzaldehyde condenses with aniline, where he reported no yield, we have found no case where *o*-bromobenzaldehyde has been condensed with an amino compound.[14] The work of others, specially that of Stewart,[15] Petrenko-Kritschenko[16] and Kehrmann[17] show that certain reactions of the carbonyl group are hindered by substituents on adjacent carbon atoms. The behavior of products obtainable by further bromination of 5-bromovanillin offered an opportunity to test this idea here, because the new derivative must have the second halogen atom in Position 2 or 6, the most favorable positions to exert steric hindrance. In addition, it was desired to learn whether the presence of an additional halogen atom would have any bearing on the tendency of the aldehyde to oxidize to the corresponding acid, the formation of stereo-isomeric oximes, or the hydrolysis of the corresponding nitrile to its acid. Such a study seemed important because only one dihalogenated vanillin has been previously

[10] Lassar-Cohn, "Arbeitsmethoden für organisch-chemische Laboratorien," Voss, Leipzig, **1923**, 5th edition, p. 47; also, *Ber.*, **28**, 1756 (1895).

[11] The failure may be due to the presence of the hydroxyl group. Irvine [*J. Chem. Soc.*, **79**, 670 (1901)] found that salicylaldehyde methyl ether undergoes the benzoin condensation in the absence of the aldehyde.

[12] Hantzsch, *Ber.*, **23**, 2776 (1890).

[13] Blanksma, *Chem. Weekblad*, **9**, 865 (1912).

[14] Although steric hindrance might be expected to interfere in such a reaction, cases are known where acceleration was observed. Fischer and Giebe [*Ber.*, **30**, 3057 (1897); **31**, 546 (1898)] obtained a very small yield of benzaldiethylacetal by treatment of benzaldehyde with an alcoholic solution of hydrogen chloride. With *o*-nitrobenzaldehyde a yield of 70% was obtained. Raiford, Taft and Lankelma [*J. Am. Chem. Soc.*, **46**, 2051 (1924)] found that a negative substituent in the *ortho* position in an aniline facilitates the formation of a diacetyl derivative under certain conditions.

[15] Stewart, *J. Chem. Soc.*, **87**, 186 (1905).

[16] Petrenko-Kritschenko, *Ann.*, **341**, 150 (1905).

[17] Kehrmann, *Ber.*, **21**, 3315 (1888).

recorded, namely, the di-iodo compound of Carles[1] for which no melting point was given, no derivatives were prepared, and which is recorded by Richter as of unknown configuration.

The dibromovanillin described below has been obtained[18] in three different experiments; by treatment of a hot acetic acid solution of 5-bromovanillin with an excess of bromine, by heating monobromovanillin and bromine (without solvent) in a sealed tube,[19] and by bromination of 6-bromovanillin.[20] The product was characterized by the study of several derivatives (Experimental Part).

Especial interest attached to the study of the oxime. Brady and Dunn[5] isolated but one of the stereo-isomerides of 5-bromovanillin required by theory, although they state that "certain negative substituents in the benzene ring seem to favor the existence of two isomeric oximes." On the basis of previous work[21] they claim that "no evidence of the existence of a second isomeride has been obtained in the case of any of the hydroxybenzaldoximes." In the present work one oxime was obtained without difficulty. Treatment with dry hydrogen chloride for the purpose of transmutation into its isomer was not satisfactory, partly because of the extremely low solubility in most solvents. Attempts to prepare

TABLE II

HYDROLYSIS OF 3-METHOXY-4-HYDROXY-5,6-DIBROMOBENZONITRILE

Reagent	Wt. of sample, g.	Time, hrs.	Nitrile recovered, g.	Acid isolated, g.
75 cc. of 5 *N* NaOH soln.	3.0	12.5	2.12	0.33
Alkali soln. + 15 g. of NaCl[a]	3.0	12.5	2.67	None
75 cc. of 5 *N* KOH soln.[b]	3.0	20	0.25	2.22[c]
Alkali soln. + 18 g. of KCl	3.0	20	1.1	1.2

[a] Spohr [*Z. physik. Chem.*, **2**, 194 (1888)] and others observed that neutral salts increased the rate of inversion of sucrose by acids, and Bowe [*J. Phys. Chem.*, **31**, 291 (1927)] has studied the question further.

[b] Much silica was removed from the glass in this experiment. An attempt to avoid this and carry the hydrolysis to completion by using a more concentrated alkali solution and heating in a copper flask was unsuccessful. No acid was isolated and nearly all of the nitrile was recovered. Possibly the copper acted as an anticatalyst.

[c] The acid isolated here will be reported later.

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[18] The experimental work here recorded was completed in August, 1925. Its publication has been delayed in order to establish the structure of the compound (see Ref. 6).

[19] We are indebted to Mr. O. H. Alderks for this method. He obtained nearly a quantitative yield by heating these materials for 26 hours at 122–125°.

[20] Indicated by Raiford and Stoesser (Ref. 6). If a hot, saturated acetic acid solution of the 6 derivative, containing a little iodine as carrier, is treated with an excess of bromine with stirring, nearly pure 5,6-dibromovanillin crystallizes out in 90% yield upon cooling.

[21] Brady and Dunn, *J. Chem. Soc.*, **105**, 824 (1914).

the isomer directly by the Goldschmidt[22] method caused the loss of the methyl radical and gave an oxime of dibromoprotocatechuic aldehyde.[23]

Following the directions of Brady and Dunn in their study of the oxime of monobromovanillin, the dibromo derivative was converted into the nitrile by boiling with acetic anhydride. Boiling the monobromo nitrile with 20% sodium hydroxide solution for an hour gave the corresponding acid. Under similar treatment, the dibromo derivative was but slightly decomposed. To test the possibilities further, 3g. samples of the nitrile were heated with alkali solution for varying lengths of time, as indicated in Table II.

In this treatment with hot concentrated alkali, it was a question whether the methoxy group might be lost by saponification.[24] Because of this possibility the nitrile recovered after boiling with alkali was tested for hydroxyl group by treatment with more than two molecular proportions of benzoyl chloride. Only one acyl radical could be introduced.

Experimental Part

5,6-Dibromovanillin.—A mixture of 50 g. of vanillin and 0.5 g. of iodine, dissolved in 400 cc. of glacial acetic acid in a suitable flask, was heated to boiling under a reflux Allihn condenser, the upper end of which was attached through a safety bottle to a water pump. About twice the calculated quantity of bromine vapor was drawn slowly into the boiling liquid while the pressure was adjusted so that liquid due to condensation of vapors filled the lower third of the condenser tube. The heating was continued for three hours and the mixture allowed to stand overnight, after which it was boiled for three hours under the conditions specified. After cooling, the solid was filtered off and washed with alcohol; yield, 62%. Crystallization from glacial acetic acid gave nearly colorless needles; m. p., 218°. The product is readily soluble in pyridine, but nearly insoluble in most other solvents.

Anal. Subs., 0.2090: AgBr, 0.2544. Calcd. for $C_8H_6O_3Br_2$: Br, 51.61. Found: 51.79.

5,6-Dibromovanillidene-aniline.—A solution of the dibromovanillin and the calculated amount of aniline in 10 cc. of pyridine[25] was heated under a reflux condenser on a water-bath for one hour. Addition of water to the cold liquid caused separation of an oil which crystallized on standing. Attempts to recrystallize this product from glacial acetic acid and from dil. alcohol caused hydrolysis. Crystallization from absolute alcohol gave amber-colored crystals which melted sharply at 147°.

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[22] Goldschmidt, *Ber.*, **16**, 2176 (1883).

[23] Tiemann and Haarmann (Ref. 4, p. 620) claim that dil. hydrochloric acid, which was used in our preparation of the oxime, will convert vanillin into protocatechuic aldehyde. We have been unable to confirm this.

[24] Stoermer and co-workers [*Ber.*, **34**, 1812 (1901); **36**, 3995 (1903)] saponified phenyl alkyl ethers. Meyer and Bergius [*Ber.*, **47**, 3158 (1914)] decomposed diphenyl ether with aqueous alkali at 300°, while Perkin [*J. Chem. Soc.*, **91**, 2069 (1907)] decomposed alizarin-1-methyl ether by boiling with barium hydroxide solution. Acidic substituents increase this tendency [*Ann.*, **174**, 259 (1874)].

[25] The use of pyridine as a solvent in this type of condensation was tested by the preparation of the unsubstituted vanillin derivative. The product agreed with that obtained by Ott [*Sitzb. Akad. Wiss. Wien, Abt IIb*, **113**, 1286 (1904)].

Anal. Subs., 0.3584: AgBr, 0.3492. Calcd. for $C_{14}H_{11}O_2NBr_2$: Br, 41.53. Found: 41.46.

When aniline was replaced by *p*-toluidine in the above experiment, the product crystallized from absolute alcohol in purple crystals that resembled potassium permanganate. When heated, the purple color changed to yellow below 100°, and the residue melted sharply at 150°.

Anal. Subs., 0.3611: AgBr, 0.3086. Calcd. for $C_{15}H_{13}O_2NBr_2.C_2H_5OH$: Br, 35.95. Found: 36.37.

Crystallization of the above-named product from benzene gave yellow leaflets; m. p., 149–150°.

Anal. Calcd. for $C_{15}H_{13}O_2NBr_2$: Br, 40.10. Found: 40.40.

Bis-5,6-dibromovanillidene-benzidine.—Three g. (1 molecular proportion) of the dibromovanillin dissolved in 10 cc. of pyridine mixed with 1.8 g. (1 molecular proportion) of benzidine dissolved in the smallest possible quantity of pyridine, was heated for one hour on a water-bath. The product was precipitated by treatment of the cold mixture with alcohol. Crystallization from a mixture of pyridine and benzene gave yellow needles which, after being dried to constant weight at 135°, were heated to 350° without melting.

Anal. Subs., 0.2781: AgBr, 0.2704. Calcd. for $C_{28}H_{20}O_4N_2Br_4$: Br, 41.66. Found: 41.38.

5,6-Dibromovanillin Phenylhydrazone.—This was obtained by heating a solution of 5 g. of dibromovanillin and 1.74 g. of phenylhydrazine in 40 cc. of glacial acetic acid on a water-bath for 30 minutes. Hot water was added until precipitation began, and the mixture was allowed to stand. The product could not be crystallized satisfactorily, but the material that separated when its hot glacial acetic acid solution was allowed to stand for several days, softened at 94° and was liquid at 102°.

Anal. Subs., 0.2408: AgBr, 0.2256. Calcd. for $C_{14}H_{12}O_2N_2Br_2$: Br, 40.00. Found: 39.87.[26]

5,6-Dibromovanillin Semicarbazone.—This was obtained by heating for one hour at about 80° a mixture of molecular proportions of dibromovanillin, semicarbazide hydrochloride and sodium acetate in pyridine diluted slightly with water to dissolve the acetate. Much of the product separated during heating; yield, 64%. Attempts to crystallize from a mixture of pyridine and benzene gave a white powder; m. p., 224°. Pyridine and water gave tan-colored needles; m. p., 204°. A portion dried in partial vacuum at room temperature gave the following analysis.

Anal. Subs., 0.2763: AgBr, 0.2897. Calcd. for $C_9H_9O_3N_3Br_2.C_5H_5N$: Br, 35.87. Found: 36.60.

A portion was heated to constant weight at 135°.

Anal. Subs., 0.6894: loss in wt., 0.1232. Calcd. for 1 mol. propn. of C_5H_5N: 17.71. Found: 17.87. Subs. (dried), 0.1522: AgBr, 0.1564. Calcd. for $C_9H_9O_3N_3Br_2$: Br, 43.60. Found: 43.73.

5,6-Dibromovanillin Oxime.—A mixture of 10 g. of dibromovanillin, 1.25 molecular proportions of hydroxylamine and the calculated amount of sodium carbonate in 100 cc. of alcohol was boiled for one hour, and the cold solution slowly added to 500 cc. of water; yield, 97%. Repeated crystallization from dilute alcohol gave colorless needles; m. p., 187°.

[26] The product obtained by the use of *p*-bromophenylhydrazine could not be satisfactorily purified.

Anal. Subs., 0.2618: AgBr, 0.3027. Calcd. for $C_8H_7O_3NBr_2$: Br, 49.20. Found: 49.20.

Attempt to Prepare a Stereo-isomeric Oxime.—One and one-half g. of dibromovanillin was mixed with 40 cc. of alcohol, the calculated amount of hydroxylamine hydrochloride and 20 drops of concd. hydrochloric acid, and heated in a sealed tube at 160–170° for 12 hours.[22] After crystallization from alcohol the product melted at 167°.

Anal. Subs., 0.2038: AgBr, 0.2475. Calcd. for $C_8H_7O_3NBr_2$ and $C_7H_5O_3NBr_2$: Br, 49.20, 51.44. Found: 51.68.[27]

5,6-Dibromo-4-acetoxy-3-methoxybenzonitrile.—When the oxime was boiled with an excess of acetic anhydride for one hour, the hot liquid diluted with two volumes of water and the mixture neutralized at once with a 10% solution of sodium hydroxide, a solid separated out. Crystals obtained from a mixture of alcohol, water and a little acetic acid melted at 169°; yield, 87.5%.

Anal. Subs., 0.2526: AgBr, 0.2702. Calcd. for $C_{10}H_7O_3NBr_2$: Br, 45.84. Found: 45.52.

5,6-Dibromo-4-hydroxy-3-methoxybenzonitrile.—The above acetyl derivative was boiled for several hours with an excess of 20% sodium hydroxide solution, and the mixture was cooled and acidified with hydrochloric acid. The solid remaining was repeatedly crystallized from alcohol. It melted at 179°, but was not quite pure.

Anal. Subs., 0.3449: AgBr, 0.4170. Calcd. for $C_8H_5O_2NBr_2$: Br, 52.11. Found: 51.45.

One molecular proportion of the above product, dissolved in 10 times its weight of pyridine, was treated with two molecular proportions of benzoyl chloride.[28] Crystallization from dilute alcohol gave nearly colorless needles which softened at 212° and melted at 215°.

Anal. Subs., 0.3628: AgBr, 0.3330. Calcd. for $C_{15}H_9O_3NBr_2$: Br, 38.92. Found: 39.05.

The nitrile specified above was hydrolyzed with alkali solution, and the acid formed was separated from the unchanged starting material. The results are shown in Table II.

Summary

1. A number of condensation products of 5-bromovanillin have been studied.

2. 5,6-Dibromovanillin has been prepared and characterized by the study of a number of its derivatives.

3. Only one of the stereo-isomeric oximes of dibromovanillin required by theory was obtained in this work.

4. 5,6-Dibromo-3-methoxy-4-hydroxybenzonitrile resists hydrolysis with alkali to an extraordinary degree.

5. The halogenated derivatives of vanillin tested in this study failed to undergo the benzoin condensation.

6. The study of these derivatives will be continued in this Laboratory.

[27] This agrees with the formula for the dibromoprotocatechuic aldehyde derivative.

[28] Einhorn and Hollandt, *Ann.*, **301**, 101 (1898)

BIOGRAPHY

G. Carroll Hilman was born in Webster Parish, Louisiana, on June 18, 1888. His early education was received in the secondary schools of his native State. The first three years of his undergraduate course was taken at the University of Texas. The last year was taken at the Louisiana State University, where he received the degree of Bachelor of Science in 1921. He received the degree of Master of Science from the University of Iowa in 1922. His second year of graduate study was spent in the Colorado School of Mines. Mr. Hilman is a member of the Society of the Sigma Xi.